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Original Article

ENDOSCOPIC BAND LIGATIONVERSUS PROPRANOLOL IN PRIMARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL BLEEDING AND IMPROVEMENT OF SURVIVAL IN HEPATOCELLULAR CARCINOMA PATIENTS

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ABSTRACT

Background & Aims: *Hepatocellular carcinoma (HCC) is ranked as the 5th common type of cancer worldwide and is considered as the 3rd common reason for cancer-related deaths. It is the most common primary malignant tumor of the liver. The effect of HCC progression and its infiltration to nearby portal tracts may worsen portal hypertension (PH) leading to acute variceal hemorrhage (AVH) worsening patient survival. The aim of this study is to compare between endoscopic band ligation (EBL) and propranolol in the primary prophylaxis of esophageal variceal bleeding and improvement of survival in HCC Patients.*

Materials and Methods: *This study was conducted on 330 cirrhotic patients all of them have esophageal varices (EVs), were divided to four groups; group I that included 60 cirrhotic patients with early stage HCC, group II that included 85 cirrhotic patients with intermediate stage HCC, group III that included 105 cirrhotic patients with advanced stage HCC and group IV that included 80 cirrhotic patients without HCC as a control group. All groups were subsequently subdivided to two subgroups; subgroup (a) that included patients who underwent EBL and subgroup (b) that included patients who received propranolol.*

Results: *The primary prophylaxis from E.V. bleeding over 24 months follow up period was significantly higher in all patients treated by EBL than that in all patients treated by propranolol in all groups (p value: 0.0343, < 0.0001, < 0.0001 and 0.0403 respectively). At the same time the bleeding attacks in intermediate and advanced stages HCC patients who received propranolol were significantly more than that in control group (p value:0.0485 and 0.0301 respectively) while there were no significant difference between group I with early HCC and control group (p value: 0.7739).*

Conclusion: *EBL in this study was superior to propranolol in the primary prophylaxis of EVs bleeding in patients with HCC. Moreover, EBL were most effective in the primary prophylaxis from EVs as well as improving survival in patients with intermediate and advanced stages HCC when compared with propranolol.*

KEYWORDS: *Non-Selective Beta Blockers, Primary Prophylaxis, Esophageal Variceal Bleeding, Hepatocellular Carcinoma, Portal Vein Thrombosis*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common disorder worldwide and ranks 2nd and 6th most common cancer among men and women in Egypt (1).Recent focus on screening, surveillance and the improvement of the different modalities of HCC management tends to change the gloomy fact of short survival and bad prognosis (2).

The most frequent complications in HCC patients are ascites, encephalopathy, systemic infections, and upper gastrointestinal bleeding (UGIB). The leading causes of death in HCC patients were hepatic failure (due to tumor progression) and gastrointestinal bleeding (GIB) (3). The overall median survival was 13 months from the date of diagnosis (4).

Acute variceal hemorrhage (AVH) always plays a role in GIB; some studies have reported that the incidence of varices is 34.5% in HCC with cirrhosis and 8.2% in HCC without cirrhosis. (3) The rate of GIB is very high in cirrhotic patients with varices and concomitant HCC (76.5%) (5).

It has been estimated that AVH contributes to mortality in 25% of patients with HCC. (6) Early detection of large Esophagogastric variceal (EGV) and primary prophylactic measures, such as administration of non-selective beta blockers (NSBBs) or endoscopic Band ligation (EBL), are important for the prevention of variceal bleeding. (7, 8)

AVH from esophageal varices (EV) or gastric varices (GV) is a devastating complication of portal hypertension (PH). The short-term mortality rate was as high as 50%, with uncontrolled active hemorrhage and recurrent bleeding (9–11).Portal vein thrombosis (PVT) is common in patients with cirrhosis. The prevalence of PVT concomitant with cirrhosisranges from 7% to 25%, the presence of PVT may worsen PH. (12)

According to 2010 Baveno V recommendations (13), NSBB or EBL are first choice for primary prevention of first variceal bleeding in cirrhotic patients. However, risk factors of AVH caused by HCC or cirrhosis are different, and PH is particularly high in patients with HCC specially when combined with PVT. Xing-Shun Qi et al. (14)stated that the most important risk factor for the development of PVT in liver cirrhosis is the decreased portal vein inflow velocity and collectively, they proposed that the use of NSBBs potentially increases the development of PVT by reducing portal vein inflow velocity, Moreover another study stated that NSBBs increase the proportion who are hemodynamically compromised, time of hospitalization, risks for hepatorenal syndrome , acute kidney injury and reduce transplant-free survival in Patients with cirrhosis and SBP who should not receive NSBBs.(15) Although the impact of NSBB for HCC patients are not entirely clear, but this issue remind clinicians to careful use of NSBB in cirrhotic patients.

Since NSBBs possible adverse effects, we have to know if the use of EBL to prevent AVH in patients with HCC is superior to NSBB or not. This needs further study to clarify. So we designed this study to evaluate the feasibility and effectiveness of using EBL or NSBB to prevent first bleeding in patients with HCC concomitant with EVs.

MATERIALS AND METHODS

This study was conducted on 330 cirrhotic patients, 250 of them have HCC and80 without HCC. They treated in the hepato-gastroenterology unit of internal medicine department atouruniversity hospital, in the period from January 2012 to March 2015.

The ethics research committee, at authors' faculty of medicine, has approved conduction of this study.

Inclusion Criteria: liver cirrhosis with HCC.

Exclusion Criteria: (1) Any contra-indication to NSBBs e.g. bradycardia (basal heart rate < 55 beats per minute), Diabetes Mellitus and bronchial asthma. (2) Any previous EBL and/or sclerotherapy, any past history of transjugular intrahepatic portosystemic shunt (TIPS) or surgery for PH. (3) Non malignant PVT (it is a well-known dependent risk factor for acute PH and AVH). (4) GV. (5) Patients with past history of AVH. (6)Any significant cardiac or pulmonary co-

morbidity and any extra hepatic malignancy

All 250 HCC patients were divided according to tumor stage to three groups in addition to 80 cirrhotic patients without HCC were taken as control group as following:

Group I: It included 60 cirrhotic patients with early stage HCC subsequently divided to *subgroup Ia* that included 40 patients treated with EBL and *subgroup Ib* that included 20 patients treated with propranolol.

Group II: It included 85 cirrhotic patients with intermediate stage HCC subsequently divided to *subgroup IIa* that included 50 patients treated with EBL and *subgroup IIb* that included 35 patients treated with propranolol.

Group III*:* It included 105 cirrhotic patients with advanced stage HCC subsequently divided to *subgroup IIIa* that included 65 patients treated with EBL and *subgroup IIIb* that included 40 patients treated with propranolol.

Group IV*:* (control group): It included 80 cirrhotic patients without HCC subsequently divided to *subgroup IVa* that included 50 patients treated with EBL and *subgroup IVb* that included 30 patients treated with propranolol.

Liver cirrhosis was diagnosed on the basis of clinical, biochemical and ultrasonographic evidence. The staging of HCC was performed according to Barcelona Clinic Liver Cancer (BCLC) that defines early stage HCC as ≤3 nodules each ≤ 3cm in child-Pugh A-B patients, intermediate stage as more than 3 nodules (multinodular) in child-Pugh A-B patients and advanced stage when there were portal invasion; lymph nodes (LN)involvement and/or extra-hepatic metastases(16,17). HCC were diagnosed by abdominal ultrasound and triphasic CT and/or dynamic MRI.

The laboratory data of all studied patients are illustrated in **Table1**.

Table 1: Laboratory Data for All Patients

Parameter		Group I (Early Stage HCC) N=60		Group II (Intermediate Stage HCC) N=85		Group III (Advanced Stage HCC) N= 105		Control Group IV (Cirrhosis Without HCC) N=80		One Way ANOVA
		Ia (EBL) n=40	Ib (Prop.) n=20	IIa (EBL) n=50	IIb (Prop.) n=35	IIIA (EBL) n=65	IIIB (Prop.) n=40	IVA (EBL) n=50	IVB (Prop.) n=30	P Value
SGPT	**Mean**	51.38	52.45	52.84	52.63	52.29	55.03	52.56	55.87	0.3085
	SD	8.251	9.445	7.778	7.986	8.062	10.11	7.952	6.822	
SGOT	**Mean**	52.05	54.40	51.90	52.17	52.14	53.55	51.94	54.77	0.6032
	SD	6.139	7.387	8.195	7.229	7.460	9.257	7.750	7.030	
S.Bilirubin	**Mean**	1.285	1.245	1.470	1.463	1.485	1.548	1.912	1.887	< 0.0001
	SD	0.1762	0.1638	0.3370	0.3049	0.3088	0.3644	0.5427	0.5981	
S.Albumin	**Mean**	3.490	3.490	3.520	3.523	3.378	3.470	3.516	3.533	0.4814
	SD	0.3678	0.3726	0.3774	0.3631	0.4292	0.3831	0.3755	0.3827	
PT	**Mean**	14.68	14.60	14.66	14.71	14.63	14.73	14.66	14.77	0.9972
	SD	0.9167	0.8826	0.8947	0.9258	0.8762	0.9055	0.8947	0.9353	

Child-Pugh score was calculated using five variables: ascites, encephalopathy, bilirubin, albumin, and prothrombin time. Each of these variables was given a value of 1, 2, or 3in order of increasing abnormality, and the values were added to determine a total. A Child-Pugh score of 5-6was considered class A, 7–9 was considered class B, and 10 or more was considered class C. The child-Pugh classification of all patients was illustrated in following table:

Table 2: the Child-Pugh Classification for all Patients according to Clinical and Laboratory Data

Parameter		Group I (Early Stage HCC) N=60		Group II (Intermediate Stage HCC) N=85		Group III (Advanced Stage HCC) N= 105		Control Group IV (Cirrhosis Without HCC) N=80		
		Ia (EBL) N=40	Ib (Prop.) N=20	Iia (EBL) N=50	Iib (Prop.) N=35	Iiia (EBL) N=65	Iiib (Prop.) N=40	Iva (EBL) N=50	Ivb (Prop.) N=30	P Value
Child's class.	A	30	15	25	20	35	20	22	18	0.0011
	B	10	5	20	10	20	10	10	8	
	C	0	0	5	5	10	10	18	4	

After initial diagnosis of HCC,all patients were subjected to upper gastro-intestinal (UGI) endoscopy and the EVswere diagnosed as small, medium sized or large.The major predictive factors of first variceal bleeding episode (high risk varices) are the size of varices, the severity of liver dysfunction and the endoscopic presence of red wale marks. (18)

Propranolol dose was adjustedto decrease the heart rate by 25% from baseline, or until the heart rate is approximately 55 beats per minute. EBL was performed every 2 to 4 weeks until EVs are eradicated. Complete obliteration is achieved in most of patients after 2-4 sessions. Early bleeding after EBL is the bleeding occurring between 24 hours and 14 days after the operation. Patients were followed through for a period of 24 months. The principal end-point was bleeding from the varices. Additional end-points included death due to variceal bleeding (19).

Statistical Analysis

The collected data were organized, tabulated and statistically analyzed using Statistical Package for the Social Sciences software (SPSS, version 13, SPSS Inc. Chicago, IL, USA). The data were presented by mean and standard deviation compared using one way ANOVA test. Also, the data were presented by frequency and percent and compared using Chi-square test or Fischer's exact test when appropriate. For analysis of survival and recurrence, the time of initial endoscopy treatment was defined as day zero. Survival rate was analyzed by the Kaplan-Meier method and log rank test. Multivariate analysis was performed using a Cox proportional hazard model. In all tests P value was considered significant if <0.05.

RESULTS

In Table 3, No significant difference regarding age and sex, among all groups.

Table 3: Age and Sex Distribution for all Studied Patients

Parameter		Group I (Early Stage HCC) N=60		Group II (Intermediate Stage HCC) N=85		Group III (Advanced Stage HCC) N= 105		Control Group IV (Cirrhosis Without HCC) N=80		
		Ia (EBL) N=40	Ib (Prop.) N=20	Iia (EBL) N=50	Iib (Prop.) N=35	Iiia (EBL) N=65	Iiib (Prop.) N=40	Iva (EBL) N=50	Ivb (Prop.) N=30	P Value
Age	Mean	50.00	50.60	51.40	49.83	50.58	51.18	51.12	52.30	0.9769
	SD	9.326	10.04	9.549	10.15	10.22	9.878	10.12	8.683	
Sex	M	26	12	35	22	40	25	30	24	0.9784
	F	14	8	15	13	25	15	20	16	

In table 4, No significant difference between all groups regarding each single etiology of liver cirrhosis, while Chronic Hepatitis C (CHC) showed as the most common cause of liver cirrhosisin each single subgroup.

Table 4: The Etiology of Liver Cirrhosis in all Patients

Parameter		Group I (Early Stage HCC) N=60				Group II (Intermediate Stage HCC) N=85				Group III (Advanced Stage HCC) N= 105				Control Group IV (Cirrhosis Without HCC) N=80				Chi-Square
		Ia (EBL) N=40		Ib (Prop.) N=20		Iia (EBL) N=50		Iib (Prop.) N=35		Iiia (EBL) N=65		Iiib (Prop.) N=40		Iva (EBL) N=50		Ivb (Prop.) N=30		P Value
Cause of cirrhosis	CHC	30	75%	16	80%	40	80%	25	71%	50	77%	31	78%	40	80%	20	67%	0.9897
	CHB	6	15%	3	15%	6	12%	8	23%	10	15%	6	15%	6	12%	7	23%	
	Other	4	10%	1	5%	4	8%	2	6%	5	8%	3	7%	4	8%	3	10%	

CHC: Chronic Hepatitis C, CHB: Chronic Hepatitis B

Table 5 showing that there were no significant differences as regards grading of EVs (small and medium or large sized) in each subgroup for all groups. At the same time the medium or large sized varices of group II and III were significantly more than that in control group IV (P value: 0.0023 and 0.0004 respectively), while there were no significant difference between group I and control group IV (P value: 0.8645).

Table 5: Esophageal Variceal Grading for all Patients

Parameter		Group I (Early Stage HCC) N=60			Group II (Intermediate Stage HCC) N=85			Group III (Advanced Stage HCC) N= 105			Control Group IV (Cirrhosis Without HCC) N=80			Fisher's Exact Test
		Ia (EBL) N=40	Ib (Prop N=20.)	Total	Iia (EBL) N=50	Iib (Prop.) N=35	Total	Iiia (EBL) N=65	Iiib (Prop.) N=40	Total	Iva (EBL) N=50	Ivb (Prop.) N=30	Total	P Value
Grading of varices as regards its size	Small	20	9	29	15	8	23	15	12	27	27	14	41	P1=0.8645
	Medium/large	20	11	31	35	27	62	50	28	78	23	16	39	P2=0.0023 P3=0.0004
Fisher's exact test	P value	0.7881			0.6206			0.4933			0.6450			

P1: p value between totals of group I and IV.

P2: p value between totals of group II and IV.

P3: p value between totals of group III and IV.

Table 6: Follow Up Findings for all Patients

Parameter		Group I (Early Stage HCC) N=60		Group II (Intermediate Stage HCC) N=85		Group III (Advanced Stage HCC) N= 105		Control Group IV (Cirrhosis Without HCC) N=80		Fisher's Exact Test
		Ia (EBL) N=40	Ib (Prop.) N=20	Iia (EBL) N=50	Iib (Prop.) N=35	Iiia (EBL) N=65	Iiib (Prop.) N=40	Iva (EBL) N=50	Ivb (Prop.) N=30	P Value
Bleeding	**Early**	4	4	4	8	5	8	5	7	P1=1.0000
	Late	4	6	5	16	6	20	5	6	P2=1.0000
No bleeding		32	10	41	11	54	12	40	17	P3=0.8083
Fisher's exact test	**P value**	0.0343		< 0.0001		< 0.0001		0.0403		P4=0.7739 P5=0.0485 P6=0.0301

P1: P value between subgroup Ia and subgroup IVa

P2: P value between subgroup IIa and subgroup IVa

P3: P value between subgroup IIIa and subgroup IVa

P4: P value between subgroup Ib and subgroup IVb

P5: P value between subgroup IIb and subgroup IVb

P6: P value between subgroup IIIb and subgroup IVb

Table 6, showing clearly that, the primary prophylaxis from AVHfrom EVs during 24 months follow up period, was significantly higher in all patients treated by EBL more than in all patients treated by propranolol in all groups (p value: 0.0343, <0.0001, < 0.0001and 0.0403 respectively). At the same time the bleeding attacks - in patients receiving propranolol in group II with intermediate stage HCC and in group III with advanced stage HCC – were significantly more than that in control group (pvalue:0.0485 and 0.0301 respectively), while there were no significance between group I with early HCC and control group (p value: 0.7739). Similarly there was no significant difference as regards the bleeding attacks between all patients receiving EBL in all groups.

Table 7: Survival Rate in all Groups during the Follow up Period

Parameter		Group I (Early Stage HCC) N=60		Group II (Intermediate Stage HCC) N=85		Group III (Advanced Stage HCC) N= 105		Control Group IV (Cirrhosis Without HCC) N=80	
		Ia (EBL) N=40	Ib (Prop.) N=20	Iia (EBL) N=50	Iib (Prop.) N=35	Iiia (EBL) N=65	Iiib (Prop.) N=40	Iva (EBL) N=50	Ivb (Prop.) N=30
Died cases	**Relating to bleeding**	2	6	4	15	7	22	5	8
	Unrelated to bleeding	3	3	11	10	19	12	7	8
Survived cases		35	11	35	10	39	6	38	14
Log-rank (Mantel-Cox) test	**P value**	P1: (between Ib, IIb, IIIb and IVb) = 0.0313 P2: (between Ia, IIa, IIIa and IVa) = 0.6184 P3: (between subgroups a and b in I,II,III)= P < 0.0001							

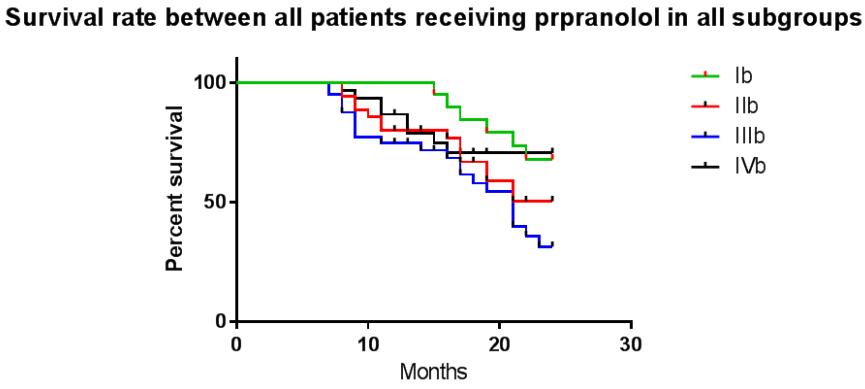

Figure 1

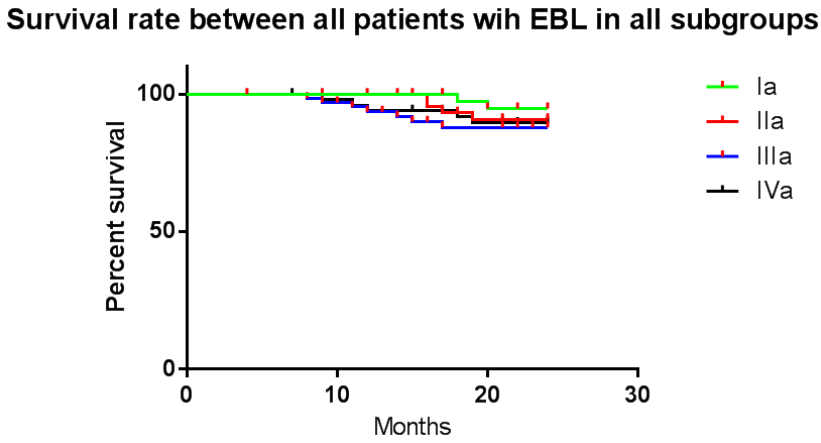

Figure 2

Table 7 showing that the mortality rate in patients receiving propranolol in group II with intermediate stage HCC and group III with advanced stage HCC due causes relating to bleeding attacks was significantly more than that in group I with early stage HCC and in control group (p value: 0.0313) while there was no difference in patients receiving EBL in all subgroups (p value: 0.6184).

DISCUSSIONS

Over the last decade, a considerable increase was observed in the proportion of chronic liver disease with HCC in Egyptian patients (from 4.0% to 7.2%). (18, 19)

Overall survival of HCC patients varied greatly between different studies. Some papers recorded considerably low survivals as 3.5 months (18) and 1.9 months in Malaysia (20) while other papers reported rates as high as 25.7 and 26.8 months in Italy and Taiwan respectively (21, 22).In an Egyptian study, the overall median survival was 13 months and EVs bleeding was the second cause of death among those patients (10.4%), however this percent was higher in other studies e.g. 21% (23) and 47% (24).

The presence of PVT may worsen PH. One of the major complications of PH is AVH. (25)In 2002, a Taiwan study concluded that PVT is indeed one of the important factors for prediction of large EGV in HCC patients. (3)

Since NSBBs i.e. propranolol possible adverse effects, we have to know if the use of EBL to prevent AVH in patients with HCC is superior to propranolol.

According to a report of the Baveno III ConsensusWorkshop on Definition, Methodology and TherapeuticStrategies in PH (26) and the American College of Gastroenterology publishedguidelines, endoscopic screening for EVsis recommended for all cirrhotic patients and NSBBs therapy is the treatment of choice for large varices (27), however application of these data on HCC cirrhotic patients still need more studies specially with the NSBBs possible adverse effects. (14,15)

In this study, CHC was the most common cause of liver cirrhosis in all groups (ranged from 67%-80%), However, CHB and other causes represented the 2nd and the 3rd cause respectively, which is compatible with data of other studies. Waked et al. (28) showed that HCV is an important (84.3% of patients with chronichepatitis), if not the primary cause of chronic liverdisease in this region of Egypt. While in another study (29), prevalence for HBV and HCV were 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases in a systematic review and meta-analysis in Egypt. From these data we can say that HCV is the most common cause of liver cirrhosis and HCC in Egypt.

In this study, Child's classification showed a significant difference among all groups. Class C and medium/large EVs were significantly more in cirrhotic patients with intermediate (II) and advanced HCC (III) than those of the early group (I).This draws our attention that properly that there is a relation between the child class and the size of the EVs.MJOrl off et al. (30)found that patients with PVT had more advanced cirrhosis as a group than patients without PVT, and more of those with PVT were in Child's class C, however Child-Pugh grade in another study, was marginally significant as a risk factors for first bleeding in HCC patients. (31)

Many studies suggested that HCC progression induces elevation of portal venous pressure and thereby enhances the risk of bleeding from EVs. (31-33) Moreover, many studies found that there were a difference in survival between those with Child's grades A and B when compared with Child's C and the functional state of the liver at the time of hemorrhage is an important prognostic factor (3, 24).

There has been some debate regarding the timing of endoscopic therapies for EVs, and whether these therapies should be used as prophylaxis or in an emergency setting. (31) In a study on cirrhotic patients, prophylactic endoscopic Injection therapy (EIS) provided a greater survival benefit than emergency. (34)

The primary prophylaxis from AVH from EVs over 24 months was significantly higher in all patients treated by EBL more than in all patients treated by propranolol in all groups (p value: 0.0343, < 0.0001, < 0.0001 and 0.0403 respectively).These results confirmed the excellent effect of EBL in preventing AVH due to EVs in patients with intermediate and advanced stages HCC. Takamoni et al (31) showed in his study that prophylactic endoscopic therapy may have a preventive effect on bleeding from high-risk EVs in HCC patients. At the same time, the bleeding attacks - in patients receiving propranolol in group II with intermediate stage HCC and in group III with advanced stage HCC – were significantly more than that in control group (p value:0.0485 and 0.0301 respectively). These results is in agree with other studies (17, 31)

Interestingly, no statistically significant difference regarding using EBL for primary prophylaxis in HCC patients and the control group, However propranolol achieved statistically significant difference in primary prophylaxis in control patients than those with HCC, which may be explained with that the effect of HCC progression and its infiltration to nearby portal tracts may worsen PH.(3)

In this study, death due to causes unrelated to the bleeding was more than death due to bleeding (58 vs 56) which is compatible with other studies (4, 25).

The survival ratio in this study was higher in all HCC patients underwent EBL (109/155, 70.3%) than those received propranolol (27/95, 28.4%) (P < 0.0001), while there was no difference in patients receiving EBL in all subgroups (p value: 0.6184)(survival in the control group was 76% in IVa and 46.7% in IVb). In a recent study, prophylactic endoscopic therapy (PETs) effectively prevented death due to bleeding as well as first bleeding; however, they did not contribute to increased survival. (31, 35) Some studies have shown that prophylactic EIS for EVs prevents bleeding and prolongs survival in patients with HCC (36, 37, 38). Moreover, the mortality rate due to causes related to EVs bleeding in patients receiving propranolol in group II with intermediate stage HCC and group III with advanced stage HCC was significantly more than that in group I with early stage HCC and in control group (p value: 0.0313).

CONCLUSIONS

The major Limitation in this study was the lack of awareness of the importance of EBLin improving the survival of those patients with HCC and PVT. Many physicians in our country don not recommend EBL as a prophylaxis for those patients; however, despite of the fact that HCC is a serious fatal disease specially if accompanied with PVT, but bleeding varices was the most common of death among patients not underwent EBL.

In conclusion, EBL in this study was superior to propranolol in the primary prophylaxis of EVs bleeding in HCC patients. Moreover, HCC patients underwent EBL had a better survival when compared with those received propranolol. The mortality rate due to causes related to EVs bleeding in intermediate and advanced HCC stages in patients receiving propranolol was higher than the early HCC stage patients.

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